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RADIUM

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VOL. VI DECEMBER, 1915 No. 3

CONTENTS

Recent Contributions to Radium Therapy 57

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A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES

RADIUM

A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY, PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES.

Edited and Published by Charles H. Viol, Ph. D., and William H. Cameron, M. D. with the assistance of collaborators working in the fields of Radiochemistry, Radioactivity and Radiumtherapy.

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VOL. VI. DECEMBER, 1915 No. 3

RECENT CONTRIBUTIONS TO RADIUM THERAPY

Winfield Ayres, M.D. (New York). The Effect of Intravenous Injections of Radium on a Persistent Positive Wassermann Reaction. Medical Record. October 9, 1915.

Nearly every physician has been at least annoyed by his inability to obtain a negative Wassermann in a certain proportion of his cases of syphilis. The writer, being no exception, wondered what effect radium would have on this condition. The histories of the following cases seem worthy of report in this connection.

Case I.—W. Y. came under my observation in 1904. He had at that time a typical cancer and later developed secondary lesions. He was treated for four years by injections, inunctions, and internal medication and then, as there had been no evidence of disease in three years, was pronounced cured. He consulted me on January 9, 1915, because his teeth were loosening, his dentist having ascribed the condition to either medicine or syphilis. The patient had shown no signs of syphilis in ten years and had considered himself cured. His blood was taken for a Wassermann more as a matter of curiosity than because syphilis was suspected. The reaction was four plus. He was given five intravenous injections of 50 micrograms of radium at two-day intervals. On January 28 he reported that he "hadn't felt so well in years," but the Wassermann was still four plus. He was then given a 50 and at two-day intervals three injections of 100 micrograms. On February 26 his Wassermann was negative. He did not report again until May 6 when he stated he was feeling remarkably well, but the Wassermann reaction was returned four plus. He was given three injections of 100 micrograms each and on June 1 his Wassermann was again four plus. Two more injections of 25 micrograms and on June 15 the Wassermann was returned negative. Since that time he has been receiving weekly

injections of 10 micrograms of radium combined with 10 milligrams of vanadium and his Wassermann has remained negative.

Case II.—J. L. contracted syphilis in 1901 and was treated about six months with mercury pills and then received some form of intravenous injection. He was pronounced cured in 1904. He came to me in September, 1913, because he had had a Wassermann taken in June and it had been returned positive. There was no sign of syphilis, but the Wassermann was four plus. He absolutely refused to take mercury in any form and he was given neosalvarsan injections—five courses of three injections of 0.9 were given at three months intervals, but this had absolutely no effect on the Wassermann reaction. On November 27, 1914, he was given 50 micrograms of radium intravenously, but owing to an accident he was unable to report again until January 20, 1915, when he was given 50 micrograms of radium. This dose was repeated on the 22d and on the 24th. On February 10 his Wassermann reaction was four plus. Three injections of 100 micrograms each were given and on March 11 his Wassermann was negative. On May 15 his Wassermann was two plus. Three more injections of 100 micrograms were given and on June 15 the reaction was negative. Since that time he has been receiving weekly injections of 25 micrograms and his Wassermann reaction has remained negative.

Case III.—C. W. contracted syphilis in 1908 and was treated for two years with mercury pills. He was referred to me on October 17, 1910. He showed no sign of syphilis and a Wassermann reaction was negative. I advised a second test and four months later it was returned four plus. I referred him to a physician in his own town for treatment, recommending mercury and neosalvarsan. He was treated for three years, but every test showed two or three plus. Beginning on January 27, 1915, I gave him intravenous injections of 50 micrograms of radium at two-day intervals until 250 micrograms had been injected. On February 27 his Wassermann was negative and has remained so since without further treatment, unless the local use of radium in his mouth for leucoplakia may have some influence on the reaction. This is extremely doubtful.

Case IV.—C. L. developed a chancre which was followed by secondaries in 1902. He took mercury pills for nine months and from that time had no sign of the disease until shortly before he was brought to me in February, 1913. At that time he presented all the signs of cerebral syphilis. His Wassermann was four plus. He was given five courses of neosalvarsan (0.9), and an attempt was made to supplement this with injections of mercury, but this had to be discontinued. The patient made a complete clinical recovery, but his Wassermann reaction was one plus or stronger on every test. On March 27, 1915, his Wassermann reaction was one plus. He was given one injection of 100 micrograms of radium and this was followed by two injections of 50 micrograms each at two-day intervals. On April 12 his Wassermann reaction was four plus. He was then given a 150, 200 and a 250 micrograms injection with the result that on May 3 a negative Wassermann was returned. Since then the patient has been in perfect health, and on every occasion his Wassermann has been negative.

In conjunction with these four cases, one case of acute syphilis and one of subacute syphilis were treated by intravenous injections of radium. Neither was in the least benefited clinically in spite of the fact that enormous doses were given.

These four cases have demonstrated that radium by intravenous

injection can change a persistent positive Wassermann to a negative. The first thought which comes to mind is that the change in reaction might be due to radium inhibiting the action of the reagents in a manner somewhat similar to alcohol, but a careful study of the cases proves this not to be the case. There seems to be some direct action on the disease. In Case IV the small dosage of radium had a provocative effect exactly like a small dosage of salvarsan. Yet neither case of subacute or acute syphilis was benefited by radium alone.

The next problem raised by these few experiments is whether the cause of the change in reaction was not due to radium activating anti-syphilitic medicine which had been given before radium was used. But Case I. had taken no medicine of any kind in seven years and it seems hardly probable that mercury could have remained in his system for that length of time.

It will require a large number of cases treated over a number of years to reach an absolute conclusion as to the benefit of producing a negative Wassermann by this method.

In these cases a solution of radium bromide was used. The dosage refers to radium element and not to the salt.

On account of the expense of treatment only private cases were treated and only those on whom I could rely absolutely to go through with the experimentation.

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K. F. Snyder, M.D. (Freeport). The Radical Cure of Cancer by Radium. Abstract of a paper presented before the Freeport (Ill.) Academy of Medicine, September 20, 1915. "In the course of his remarks Dr. Snyder said:

"It will be unnecessary before this meeting to go into the question of the efficacy of radium in the altering of morbid growths in the human body. You are all too well aware of the arguments that have been made both for and against this element in the cure of neoplastic troubles in various parts of the body for me to enlighten you on either phases of the question. I am, however, at the present time in a position to speak from my own experience in the use of radium in the treatment of these various growths in numerous parts of the body and I shall occupy your time but briefly in running over the cases that I have treated with their results."

"I will say in passing that one meets with a great deal of skepticism and prejudice in the use of radium in curing malignant trouble, and I will admit that before my own personal experience was begun I was of those who put little faith in the use of radium. However, since I have experienced its various manifestations upon numerous types of disease the evidence to my own mind has become so overwhelming in regard to its usefulness that I have become very enthusiastic, as I have under my own personal observation seen many cases that undoubtedly have been cured, which otherwise could not have been influenced either by knife, cautery or X-ray."

"I have treated up to date some twenty cases of epithelioma in all stages of advancement, from the very incipiency of degeneration in a wart to the ulcerated surface of a broken down epithelioma, and while of course the length of time has not been sufficient to say absolutely in many of these cases that the growth will never return, yet in view of their appearance and the lack of metastatic growth at the time of the beginning of treatment and the history of other cases which have shown

similar results but of longer standing I feel that one is very safe in saying that the condition will never return at least upon the site of their removal, I have persuaded some of my patients to present themselves before you this evening that I may illustrate the exact results that we get in the treatment with this element."

"The error that is commonly made in the treatment of malignant growths is, first, attempting to do too much with a small amount of radium; second, promising results where metastasis have already occurred, or where the general system has been invaded by cells which have left the original seat of trouble and are disseminated through the body; third, by not using proper methods in crossfiring the growth."

"It has been claimed by some users of radium that there are certain classes of growth that seem to flare up and increase in growth from its use. It has not been my experience thus far in any case that I have treated. In fact I have yet to see the case treated with radium that has not immediately shown an improvement, and in most of the cases an improvement which has extended eventually to an apparent cure of the condition. I will say, nevertheless, that no case of epithelioma should be treated with radium, where it is in a portion of the body large enough that large amounts of the tissue may be removed with the growth, thus surely extending beyond the range of cell metastasis. On the other hand, when it involves the treatment of a new growth about the nose or the eyes or in general about the face or the bony structure, lobes of the ear, etc., radium is the method of choice without any question."

"Cancer can be cured when these conditions are properly met. The cases that I have undertaken range as I have said from those in the very incipiency of growth to broken down tissue. The areas involved have been the prostate, the orbit of the eye, the bridge of the nose, which by the way appears to be the most common site, for these cases that yield most readily to radium, the uterine cervix, the lip, the breast, over the sternum, the alveolar process of the lower jaw, the finger and various other portions of the body. I might well also include in this list numerous cases of warts which have undergone degeneration, pigmented moles, birth marks, and general abnormalities of cell growth."

"I have had no failures in any case of simple growth of non-malignant nature and I have seen some very bad cases clear up absolutely. I have seen a number of instances of carcinoma of the cervix which have gotten well without any question, melting away like ice before the sun and the bleeding fungoid mass disappearing, giving place to perfectly normal tissue. I have seen perforating ulcers of the nose disappear like magic, healing over and getting a surface which has epithelized to an extent that you could hardly believe that anything existed there before. One instance of an epithelioma originating over the bridge of the nose. which had invaded the canthus of the eye and had begun destroying the lower lid and involved the conjunctiva has healed with the greatest kindness. It is difficult to believe that such a condition ever existed there before. One massive application of radium to the interior of the cervix has had the most wonderful effect in curing entirely most intractible cases of idiopathic metrorrhagia. Birth marks have under my eye disappeared completely and all in all there cannot be the slightest doubt that in this element we have the most wonderful power of correcting disordered cellular function."

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Worthington Seaton Russell, M.D. (New York). Physical Agents in the Treatment of Cancer. International Journal of Surgery, XXVIII, pp. 245-7, July, 1915. "Among these procedures are to be included the physical agents, most of which, with the exception of the X-ray, radium, and other radio-active substances, utilize the electric current of heat. The most important are the fulguration of the de Keating-Hart, destructive fulguration, the electro-thermic coagulation of Doyen, the desiccation of Clark, thermo-radiotherapy, the Percy method, as well as other cauteries. Brief mention only can be made of these different methods; for a full description the reader is referred to "The Cancer Problem," by Bainbridge."

Speaking of radium Dr. Russell says, "Although in use for a number of years, both abroad and in this country, radium has hardly reached its level in the treatment of malignant neoplasms. Like all new methods, it has its enthusiastic advocates, who see in it the agent that will revolutionize the treatment of cancer, while on the other side are those that condemn, oftentime without fair and thorough trial. The final decision must be made by those who use the substance with enthusiasm tempered by scientific scepticism. It will take some years before the final decision can be reached. Improved technic, a larger dosage and a dosage calculated to meet the particular type of growth under treatment will probably help to secure better results. Reports from many observers show that radium will cure angiomata, keloids, and kindred conditions, and will often cause the disappearance of certain superficial malignant neoplasms. In deep seated carcinoma the remedy is still on trial. The prophylactic raying of the operative field has been tried at the London Radium Institute, but a sufficient length of time has not elapsed to judge of its value. The writer has one case operated upon by Dr. Bainbridge over a year ago, in which an incomplete operation was performed for carcinoma of the breast, as the patient refused a complete amputation. At the time of operation radium was buried in the wound where the mass had been removed, and as soon as the wound had healed the entire side of the chest was given a series of exposures to radium. There is no evidence of a recurrence."

"Various combinations of these methods, with and without operation, are being tried, but it will take years before their value can be determined."

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Howard A. Kelly, M.D. (Baltimore). The Radium Treatment of Fibroid Tumors. Surg. Gyn. and Obst. XX, pp. 271-3, March, 1915. A series of thirty-six cases of fibroid tumors of the uterus were treated with radium. Only cases which presented some serious complication, such as pelvic inflammation, ovarian growths, or obstructive symptoms, were excluded from this treatment. The method of treatment employed has been a dilatation of the cervix and the introduction within the uterine cavity of amounts of radium varying from 30 to 724 mg. In some of the larger tumors an additional massive treatment has been given through the abdominal walls. From the results he concludes that massive radium treatment of uncomplicated fibroid tumors is the best plan, as it stops the excessive flow; sometimes in younger women it regulates it without stopping it. Radium reduces the tumors in almost every instance, relieves pressure symptoms, and even causes large tumors to disappear. A fibroid tumor is not a malignant growth; therefore any method of treatment which will give entire relief to the symptoms is the best method, provided it will at the same time avoid the various

risks of an operation. If radium is tried and fails, the operation can then be undertaken without any added risk. While a recent radium treatment often makes more difficult the subsequent radical extirpation of a cancer of the cervix, there is no reason to expect this result in fibroid tumors. The writer believes that with increased experience and improved technic, it will be possible to relieve every patient of hemorrhages, and in most instances to do away with the tumor (say in nine cases out of ten), and that without serious discomfort, risk, or confinement to bed for more than one or two days. Patients too anemic and weak even for an intrauterine application of radium can be treated through the abdomen exclusively.

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"Radium Treatment of Uterine Cancer.—Adler operates in all operable cases, but when this was not possible he has found radium treatment of great benefit. The technique is strickly individualized, the dosage moderate. In the last few months he has made a practice of prophylactic exposures after operating. He begins it about the tenth day, continues at four weeks' intervals, using at most 50 mgm. at a ten hour sitting. He makes a point of testing the susceptibility of the patient, placing on the skin capsules with varying amounts of radium and with various filters, thus determining the individual erythema dose. As much of the inoperable growth as possible is removed, and then after an interval of two or three days, five exposures are made, each for twelve hours, the intervals between the exposures ranging from twelve hours to several days, according to the local and general reaction. A second and a third series are then given after suspending for three or four weeks. The amount of radium used varied from 29 to 50 mg."

"Thirty-four patients have been given radium treatment on these principles, and of the 18 who have completed the course, one had died since from abscesses in the lungs; 3 were not benefited or merely improved, but the 14 others are clinically cured. This includes 9 cases of cancer of the cervix; 2 of the body of the uterus; 2 of the rectum and 1 of the vagina. All were inoperable except in one case in which the patient had refused an operation; it was contra-indicated by severe diabetes or obesity plus age in the others." J. A.M.A. April 3, 1915.

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"Pozzi, S., and Rouhier, G.: Vaginal Hysterectomy Supplemented by Radium Therapy for Cancer of the Uterus. Rev. de gynec. et de chir. abd., 1915, xxiii, 209. Pozzi and Rouhier think that the extensive operation for cancer of the uterus, as practiced by Wertheim and others, has been carried too far. The immediate mortality is very high; even with the surgeons who have made a specialty of the operation and whose results are the best, the operative mortality is 15 to 16 per cent., and taking the average of the mortality statistics it is from 25 to 30 per cent. In spite of the fact that it is such an extensive and serious operation, it is very often not complete. Practically all the glands of the pelvis receive lymphatics from the neck of the uterus; therefore a complete dissection of the pelvis would be necessary to be sure of reaching all infected glands; this is manifestly impossible. The operation itself opens up large cellular spaces through which the infection may spread.

In view of the above facts the authors advocate a more conservative operation for cancer of the uterus, and they believe the best results can be obtained by vaginal hysterectomy followed by radium treatment. They do not advocate the use of radium alone, except in inoperable cases, neither do they advocate its use before operation, because the rays produce fibrous cicatrical tissue which makes the operation much more difficult; but used after operation, so that all the force of the rays may be concentrated on such microscopic remnants of tumor cells as may be left after the removal of the mass of the tumor, they have found it very effective. They filter the rays so that only Dominici's ultrapenetrating rays are allowed to pass.

They describe in detail the technique that they employ, giving a number of illustrations of the operation. They emphasize the importance of curettage and cauterization as a preliminary to the operation, and describe their method of inserting the radium tube in the drainage immediately after the operation." Surgery, Gynecology & Obstetrics, October, 1915.

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A. Richards. Recent Studies on the Biological Effects of Radioactivity. Science. XLII, pp. 287-300, Sept. 3rd, 1915. "Thus far, however, clinicians have been chiefly concerned with the formulation of effective methods of treatment, and it has been left for the biologists rather than the physicians to analyze the effects of radioactivity upon living matter."

"The attack on the problem of the effect of radioactivity on tissues and organisms and the use of radioactivity as an experimental means of studying questions of more fundamental biological importance was at first insignificant. Even yet our knowledge of the effects is very meagre; and to our ignorance of the deep-lying basic principles which govern the action of radium and of X-rays is due the uncertainty with which the extension of the methods to new fields and new problems is viewed by many medical men. The analysis of the effects has been taken up only recently and progress in the investigation has not been rapid, with the result that very little constructive work has been done."

"In general, it may be said that when living cells are exposed to action of radioactivity, the vital functions are retarded or depressed and a permanent injury may result; this depends on three factors, the strength of the radiating substance, the duration of the exposure, and the distance of the object from the source of radiation. When the intensity of the radiation is great, owing to exposure at short range to a strong preparation (or strong current in the case of X-rays) for a long time, the effects are much more injurious than when the intensity is less. Indeed, numerous cases have been reported where a qualitative difference results from a slight radiation as contrasted with one of great intensity, for frequently stimuli which will retard growth if of high degree, will be found to accelerate it if weak enough. Exposure to rays of great intensity has been shown to retard or stop growth, differentiation and regeneration, and to interfere with the processes of cell division, sometimes causing degenerative changes to take place in the nuclei, and in one case at least to induce amitosis where indirect cell division had normally been the method of multiplication. In rapidly growing tissue, such exposure will cause a decrease in the rate of division as well as interfering with its regularity. On the other hand, an exposure of

short duration and of slight intensity will in some cases stimulate growth, and accelerate regeneration, and may perhaps cause an increase in the rate of cell division."

"Of the early experiments those of Perthes, of Schwarz and of Schaper have perhaps had the most bearing on the later development of the problem. These early investigations were done about 1903-05. The pioneer stage of the investigations may be considered to end with Gager, who has been the most important botanist to make contributions to this subject."

"The work of Schwarz is of importance because from his experiments he erected a hypothesis, the lecithin hypothesis, to explain the destructive effects of radioactivity. His hypothesis was based on the fact that egg yolk is decomposed by exposure to the radium radiations. According to Schwarz the effect of radiation on chromosomes and other cell organs is an indirect one where it occurs at all, being brought about as a secondary result of the decomposition set up. It is especially at this point that the lecithin hypothesis comes into conflict with that of Hertwig, to be discussed later."

"Perthes' observations were among the first from a biological point of view. He exposed *Ascaris* eggs to radium and noted that the cell divisions became slower than in the controls, where no exposure had been made. The controls gave rise largely to active worms, but radiated eggs developed only into irregular cell-masses or misshapen little worms which were especially irregular at the tail end, the results depending upon whether stronger or weaker intensity of radiation was used. He says that all three elements which normally take part in mitosis were formed. Centrosomes, spindles and fibers were alike all clear in the experiment and in the controls. The chromosomes divided irregularly, and in *Ascaris megalocephala univalens* the characteristic number was doubled, knotty swellings appeared on the chromatin loops instead of the normal arrangement, and in some places the chromosomes were broken up into numerous unequal pieces. The injury to the eggs expressed itself in the slowing down of the development, which gives rise to abnormal individuals. The results with X-rays were entirely analogus to those with radium, delaying cell division and giving rise to abnormal products of development."

"Schaper exposed frog eggs as well as *Triton* embryos to radium for varying lengths of time. He observed an inhibitory effect on cell division, on embryonic differentiation, and on growth. There was also an inhibition of regeneration which was recognized after a longer or shorter period. The latent period usually lasted almost a day, the duration depending on the intensity of the radiation and on the stage of development of the organism. The period of development was always more or less retarded and prolonged. Finally it reached a standstill and then death resulted. He thinks there is some relation between the manner of solution of the yolk and the effect of the radiation. In older larvae, the living substances were used up and acute regenerative changes in the cell set in."

"Gager reviews the literature on this subject up to 1908 and summarizes the state of knowledge at that time in his last paragraph as follows:—

"The broadest, and at the same time the most definite generalization warranted by the work so far done is that the rays of radium act

as a stimulus to metabolism. If this stimulus ranges between minimum and optimum points, all metabolic activities, whether constructive or destructive, are accelerated, but if the stimulus increases from the optimum towards the maximum point it becomes an over-stimulus, and all metabolic activities are depressed and finally completely inhibited. Beyond a certain point of over-stimulus recovery is impossible, and death results."

"His review of the previous investigations he brings together in the following statements:

1. "Radium rays have the power to modify the life processes of both plants and animals."

2. "Roentgen rays and radium rays produce similar physiological results."

3. "Sensitiveness to these rays varies with the species of either plant or animal."

4. "Younger, and especially embryonic tissues, are more sensitive than those more mature."

5. "With only one or two exceptions, exposure to radium rays has been found to either retard or completely inhibit all cell activities. The rays may cause irregularities in mitosis."

6. "Experimental evidence for or against the existence of a radiotropic response is conflicting."

7. "Whatever the immediate, internal change produced in the protoplast may be, the result, with animals as well as with plants, appears to be more or less profoundly modified by the presence of chlorophyll in the cell.'"

8. "Radium rays appear to retard the activity of enzymes."

"Since the publication of Gager's results on the effect of radium on plants a large amount of work has been done in the laboratory of Oskar Hertwig at Berlin. Hertwig himself, his son Guenther, and his daughter Paula, and a number of his students have performed an extensive series of experiments over a wide range of forms and have obtained results which are of the greatest significance. In all of their work, radium compounds have been the source of the rays used for experimental purposes. As a strong exposure to radioactivity is always injurious to tissues, and since the development of injured eggs gives rise to malformation and produces monsters of various degrees of deformity, much of the experimental work is teratological in nature. This is interesting from a pathological standpoint, but is perhaps less fundamental than the effects of the radiation on cells (e.g., egg cells) and on their activity. On both these phases of the study the work of the Hertwigs has an important bearing."

"Recently Oskar Hertwig has brought together in a brief statement the facts most important from his interpretation which have been obtained as the results of the investigations in his laboratory. The following facts are emphasized by him:

1. "Fertilized *Ascaris* eggs, which had been radiated several hours showed pathological nuclear division figures in which the chromatin bodies are represented by irregular masses of chromatin granules. They divide slowly and begin at last to degenerate by caryoolysis. (Paula Hertwig).

2. "By intensive radiation of several hours' duration, sperm threads of the sea-urchin are so effected that, while they are able to fertilize the egg and to stimulate the egg nucleus into spindle formation, they lose

their ability to form normal chromosomes and thus are eliminated from development partially or completely on the degree of the injury. (Guenther Hertwig).

3. "An elimination of the sperm nucleus which is derived from intensively radiated sperm threads has been observed during the first and second divisions in eggs of the frog (Paula Hertwig) and of the trout (Oppermann)."

4. "For the elimination from the development process of the radiated sperm chromatin which has lost its capacity to develop, the fact established beyond doubt for the radiated larvae of *Triton* speaks convincingly, that the somatic nuclei have only half, or the reduced, number of chromosomes. Since the male chromosome complex fails to take its part in the development, due to the radiation, the somatic nuclei have only the female complex. (Oskar Hertwig)."

5. "This fact agrees with the result obtained for frog, toad, *Triton* and trout embryos, and after the maximum radiation of the sperm, which are to be used for fertilization, the nuclei of the different cells are strikingly smaller than are those of the controls of the same age, and both their surfaces and their volumes are in the ratio to those of the control as 1 : 2. For the conclusion, that the chromosome number of the nucleus is the haploid, may be drawn from the fact established by numerous experiments that the volumes are reduced almost to half. (Oskar Hertwig, Guenther Hertwig, Oppermann)."

6. "The results obtained from cytological investigation offer the possibility of explaining a fact highly remarkable from a physiological standpoint and at first glance a very puzzling one, that eggs, which would ordinarily fail to develop from the germinal vesicle stage when fertilized by foreign sperm, because of the union between disharmonious idioplasms with its disasterous consequences is avoided by the injury to the radiated chromatin, although the sperm thread penetrates into the egg and stimulates development. Although the radiation of the strange sperm has been destructive to the sperm, it has been favorable to the fertilized egg, just as in the living body a poison substance is counteracted by another poison."

"The investigation of radiation effects on Ascaris eggs was undertaken by Frauelein Paula Hertwig in order to obtain definite evidence on the facts at the basis of the biological hypothesis. Her conclusion is that the division of the eggs is retarded, and pathological appearances are very soon noticeable after the radiation; chromatin is strongly affected, as already stated, although the centrosomes, spindles and other cell organs show no injury; unfavorable action of the cytoplasm is not to be assumed since no change can be seen. She is able to find no ground for the lecithen theory, but interprets her facts from the contrary viewpoint."

"Guenther Hertwig, following the lead of his father, in his various studies set up four series of experiments, the A, B, C and D series. In the A series, eggs were radiated in the two-cell stage, or after fertilization; in the B series, sperm were radiated and then used to fertilize normal eggs; in the C series, eggs were radiated and then fertilized by normal sperm; in the D series, both eggs and sperm were radiated before fertilization. The experiments described in his first paper were on the frog's eggs. He found that in the C series (normal sperm by radiated eggs) the injury increases with the duration of the radiation up to a maximum, and from there on decreases again as the radiation is pro-

longed. Only the radiated nuclei show the effects, and there is no evidence for the hypothesis that yolk which contains lecithin is being broken down. The injury is greatest on young tissue and on tissues which are to be highly specialized; it is productive of manifold disturbances of the developmental processes. In the frog development is possible with only a haploid nucleus, that is, only the half of the nucleus derived from one parent. Where the injury is severe to either the egg or sperm nucleus, the other is able to carry on the development, and in fact there is less interference with the regular course than in the case where both take part in the process, for here the injured half is no longer a factor; it is able only to stimulate development and then is eliminated from the process. In other words from the standpoint of heredity, this is a case of parthenogenesis. For the spermatozoon always has two functions to perform: it must initiate development, and it must carry the inheritance from the male line. In this case only the first function is accomplished, and parthenogenesis is the virtual result, the male pronucleus being eliminated from development by failing to unite with the female pronucleus. This result is important as evidence that the nucleus is the bearer of the inheritance substance and that in the beginning of development male and female nuclei are of equal significance."

"Subsequently Guenther Hertwig performed a similar set of experiments on the eggs of the sea urchin. Here he was able to work out the cytological details of the process and to establish firmly his view just stated, that the eggs after intense radiation undergo parthenogenetic development. This is the most important point of his contribution, although he presents much evidence for the biological hypothesis."

"In America, although much attention has been given to the medical aspects of radioactivity, very little work on the biological phases of the problem has been attempted."

"Packard has recently published an account of his experiments on the effect of radium on the fertilization of *Nereis*. These experiments were performed to ascertain how 'early the development of the egg is affected by radium radiations when (1) the sperm is exposed; (2) when the egg is exposed; and (3) when the egg is exposed immediately after fertilization.' His results are important, for he finds that, in addition to the usual effects such as retardation of development, multipolar spindles and the like, not only chromatin, but also the achromatic portions of the spindles and the cytoplasm, show the effects of the exposure. In eggs radiated before fertilization, it may happen that the alveolar layer of the cytoplasm is not extruded as is normally the case in the eggs of *Nereis*. If this occurs the maturation processes are much modified, resulting in diverse forms of chromosomes and spindles, with perhaps small asters scattered about through the cytoplasm; and various other irregularities may be present in the mitotic figures. Thus it will be seen that Packard's observations do not all agree with those made in Hertwig's laboratory. Parthenogenesis is not found to occur in *Nereis* as the result of exposure to radium, but it is a common observation that the eggs of that animal are not as favorable for pathenogenetic development as are those of the sea urchin upon which Hertwig worked."

"For various reasons the hypothesis of both Hertwig and Schwarz are held to be insufficient to account for the phenomena observed by Packard, and he proposes another explanation, suggesting 'that the radium radiations act indirectly on the chromatin and protoplasm by activating autolytic enzymes which bring about a degeneration of the

complex proteids, and probably by affecting other protoplasmic processes in the same manner.' This hypothesis is reached partly as a result of his own experiments, and partly from a consideration of certain other work, and to some extent takes a middle ground between the other two, although in some phases it differs sharply from both. Cells contain a great many kinds of enzymes and it has been shown by a number of investigators that radium rays and X-rays have the property of modifying the action of some enzymes. Packard concludes that while many enzymes may be activated, 'the lytic enzymes are more stimulated than those which play a synthesizing role.' Where a slight radiation results in acceleration, the synthetic processes may be supposed to be stimulated more than the destructive activities. This hypothesis is essentially chemical in nature and seeks to explain the morphological effects observed in the cells as the indirect result of enzymotic activity under the influence of the radiation."

"Various new arguments for and against these hypotheses and theories have been brought out as new facts have developed. It is, therefore, necessary to consider the more important points critically."

"The lecithin hypothesis was established on the basis of an experiment by Schwarz, showing that in the chicken egg yoke, containing lecithin, is broken down under the influence of radium. Against this hypothesis numerous objections are now to be raised. Hertwig pointed out that the decomposition was not determined by strict chemical methods, and Neuberg also criticizes it on chemical grounds, for lecithin is itself so unstable that only a very accurate chemical study could determine whether its decomposition was actually due to the radium radiation."

"If the seat of the injury were in the yolk, little effect could follow radiation of the sperm before fertilization, for the sperm at most contains but little lecithin, and contrarily, much greater injury should result when the egg is radiated. As a matter of fact there is very little difference between the results on the embryo, whether it is the egg or the sperm that is radiated before the fertilization. Egg nuclei are equally capable, with those of the sperm, of contributing the chromatin by which the parthenogenetic development previously described takes place, both at first are able to start the development of the egg so far as the heridary units are concerned, and injuries arising from the disturbance of either are equally great."

"Very little lecithin could be decomposed when so short a radiation of the sperm as a minute was employed, as by G. Hertwig; yet this radiation was sufficient to cause marked departures from the normal in the embryo. That no chemical poison is generated by lecithin decomposition is obvious, for in the case of the short radiation of the sperm the poison would be too dilute to cause effects equal to those resulting from longer radiation of the egg."

"The lecithin theory takes no consideration of the fact that the most careful cytological study shows no morphological evidence of yolk destruction; nor of the fact that nuclei and especially chromatin do suffer marked changes as the results of the radiation. On the latter point all investigators agree, and it must be explained by any hypothesis which seeks to account for the changes produced. Furthermore, yet other cell constituents are acted on by radiation, for cell extracts and cell enzymes have been shown to be activated or retarded in their action, depending upon the conditions of the experiment."

"In this connection, it is by no means clear how lecithin decomposi-

tion within the egg could prevent, as Packard found radiation to do, the extrusion of the alveolar layer of the cytoplasm, a phenomenon depending upon activities at the surface of the egg. And finally, it is not possible to account on this basis for the elimination of the sperm head from development, or for the fact that somatic nuclei of radiated *Triton* embryos contain only half or the reduced number of chromosomes."

"Most of these arguments against the lecithin hypothesis were, of course, unknown at the time it was proposed. They are so much at variance with it, however, that it seems impossible to give it further serious consideration. It may be regarded as completely overthrown."

"The objections to Hertwig's biological hypothesis are less serious than in the case just discussed, and they would scarcely hold against it in a less extreme form. It is, of course, true that the solution offered by Hertwig is incomplete in that it does not go far enough back into the organization of the cell; for, even on the assumption that the chromatin is the chief seat of injury, further explanation which must ultimately be chemical in nature, is required to show how the injury is communicated to other parts of the cell and what the mechanism is by which its action is manifested."

"According to the Hertwig hypothesis, chromatin above everything else in the cell suffers injury from radiation and the pathological conditions in the embryo are traceable to the injured chromatin, which may be regarded as a 'contagium vivo' increasing, ferment-like, at each division. Thus the mechanism of the cell provides the means for distributing the injury to each successive cell generation and for carrying it to all parts of the embryo."

"To this theory, Packard has offered two criticisms. The concept, that the injured chromatin or a substance produced from it acts as a contagium vivo, is scarcely a solution of the problem, for it merely restates in another form certain facts observed and presents a picture of the problem itself from a different viewpoint without giving any explanation of the facts. It should again be pointed out that the ultimate solution must be chemical in nature. Packard also questions the assumption that the injurious substances developed in the nucleus must remain there and cannot involve purely cytoplasmic structures even during division (for a normal haploid division of the egg chromosomes takes place if the radiated sperm head does not mechanically interfere in the spindle). A condition contrary to this assumption is given by Packard, showing that cytoplasmic structures are changed in *Nereis* eggs, for example in the case of eggs radiated before fertilization which fail to give off the alveolar layer and thus extrude the jelly as they should do. Obviously here the injury has been communicated to the egg cytoplasm, and is not in accord with the Hertwig assumption."

"But the most serious objection to the Hertwig theory as it now stands lies in the fact that other than nuclear structures and substances are affected by X-rays and the radium rays. The failure to extrude the alveolar layer in *Nereis* eggs is a case in point, and in the same eggs abnormal spindles and asters occur as a consequence of radiation. It has been found by numerous investigators that radium rays have the power to effect enzymes, and the writer has shown that X-rays are able to bring about modification in the activity of certain enzymes. Enzymes are derived from living tissues, and if it is possible to cause their modification outside of the cell by the use of radioactivity it is not improbable that they also undergo change while within the

cells. In fact, the writer working with Miss Woodward was able to prove that X-rays can be used to influence the activity of the cell extractive called fertilizin. This substance is extracted from sea-urchin and starfish eggs when the ripe eggs are allowed to stand in water for a short time, and it possesses the property of causing the agglutination of the sperm of its own species. Its behavior is in some respects comparable to that of an enzyme and it is possible that the substance contains enzymotic bodies. The experiments showed that radiation by X-rays is capable of changing the activity of fertilizin, and in general agrees with previous work that weak radiation is accelerative and strong inhibitive. Fertilizin is a substance derived from the living eggs and the extraction takes place while the egg is in the resting stage; sometimes even in the germinal vesicle stage; at this stage chromatin can scarcely play any part in the giving off of fertilizin. In this case, then, the radiation has had a considerable, and a measurable, effect on a cell substance independent of the chromatin or other nuclear structures. This fact can hardly be brought in line with the Hertwig hypothesis in its present form."

"Yet it is true that chromatin and nuclear structures are greatly changed by radiation. In any true explanation that may be given this important fact must be dealt with. It is possible that a modification of the present form of the Hertwig theory in which the effect on enzymes is recognized may be sufficient to account for all the facts that are now known."

"Packard has attempted such a modification in his suggestion 'that the radium radiations act indirectly on the chromatin and protoplasm by activating autolytic enzymes, which bring about a degeneration of the complex proteids, and probably by affecting other protoplasmic substances in the same manner.' Against this hypothesis there is little that can be urged except the fact that it rests upon insecure evidence there being but few actual observations or experiments which contribute to it. It is certain that radiation influences the activity of various enzymes, but there is very little evidence upon which to base the assumption necessary to the hypothesis that those enzymes which cause katabolic changes in the cell proteids are accelerated to a greater extent than those which have the opposite function. For this reason judgment can only be suspended until such a time shall come when accurate and more abundant data are at hand for attacking the problem."

"Joly has proposed a different kind of explanation to account for X-ray effects. Comparing the events which take place in a photographic film with those which occur in cells subjected to gamma or to X-rays, he supposes that the rays increase ionization in the tissue. The various results found are accounted for as due to differing degrees of ionization and to the presence or absence of an 'intensifier' or an 'inhibitor.' No evidence from biological studies is given to support this hypothesis, however; it must, therefore, wait experimental confirmation."

"It will be seen from the foregoing review that all the investigations which have contributed to the development of these various theories either have had a morphological basis or were of a chemical nature. Along these lines there remains a great deal to be accomplished; we especially need more exact information on the nature of the injury which is done to the chromatin and to the cell organs."

"But in addition to the morphological study the general problem must be studied by other methods. The question is raised as to what is the nature of the stimulus by which radioactivity affects organisms.

According to Verworn a stimulus is 'any change in the external agencies that act upon an organism.' Are the rays of radium or X-rays comparable to the electric current, for example, in the manner in which they affect protoplasm? An experiment was performed by the writer to gain information on this point. A frog's leg was set up as a muscle-nerve preparation; when stimulated electrically it was found to react normally. The nerve, and later the muscle directly, were exposed to X-rays. When the brush discharge was carefully screened away from the preparation, the X-rays were unable to cause any contraction, even of the slightest extent, as shown on the drum of kymograph. While it gives no information as to real nature of the stimulus, it indicates that the stimulus of radioactivity is not comparable in its effects with that of the electric current."

"Gager has adapted Verworn's biogen hypothesis to explain the manner in which radium rays act as a stimulus to organisms, and to provide the mechanism by which the stimulation may be supposed to operate. A stimulus is any change in the external agencies that act upon an organism. Metabolism, according to Verworn, depends upon the continual destruction and continual reconstruction of a very labile chemical compound, biogen, which 'develops at an intermediate point in metabolism, and by its construction and destruction comprehends the sum total of metabolism.' It is not a protein nor living, for a molecule can not be alive. The ratio of construction and destruction of biogen molecules under normal conditions of equilibrium is $\frac{\text{construction}}{\text{destruction}}=1$. Therefore, 'the irritability of living substances depends upon the lability of the biogen molecules."

"Gager points out the probability that radium may not affect their stimulation 'by acting directly upon the biogen molecules, or whatever the reality may be that corresponds to this term, but by acting upon other substances in the individual cells, or by modifying some process either preceeding or following the elaboration of the biogen molecule.' The rays may produce their effect indirectly by acting upon some non-vital constituent other than the biogen, or upon some purely chemical process. Thus does he conceive the mechanism by which the rays produce the changes which they effect on organic bodies."

"From Gager's conclusions that radioactivity is a stimulus to metabolic processes, it may be inferred that the functions, as cell division, which even remotely depend on these processes would also be affected by radiation. Such an inference is borne out by the observations made by the writer on the rate of division in *Planorbis* eggs that had been exposed to X-rays, for in these experiments it was found that a light radiation served to accelerate the first one or two mitotic cycles that followed it; after that injurious effects gradually asserted themselves. A strong radiation was directly inhibitive. The cytological study of the eggs used in these experiments has not been completed, so that it is as yet impossible to correlate the observations on the living eggs with changes in the finer details of their structure. It is of course possible that we have manifested in these physiological processes influences that make no impress on the morphological structure of the egg."

"The case of the influence of X-rays on fertilizin, already referred to, provides another instance where the effects are without direct morphological representation. Doubtless others occur. These cases

must of course be accounted for by any explanation of the effect of radiation on living organisms."

"The facts, as they are at present known in regard to the effects of radioactivity on living matter, show that life processes are subject to marked changes under the influence of the radiation, a slight exposure being accelerative in most cases, while a more intense treatment is inhibitive or destructive. As a causal factor in these effects, the demonstrable injury to the chromatin of the cells is undoubtedly important; but there are also good evidences that the modifiability of enzymes under the action of the rays likewise plays a considerable part either directly or indirectly in the resulting injury."

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Renon, Degrais and Tournemelle. Radium versus Roentgen Ray Treatment in Splenomyelogenous Leucemia. Bulletins et memoires de la societe medicale des hopitaux de Paris, March 1914. "The authors assert that the results obtained by them with radium in splenomyelogenous leucemia in the last four years prove this agent to be among the most useful now at hand for the treatment of this disease. Twenty-five cgm. of radium sulphate were applied over the splenic region for a day at a time in each case treated, and the rapidity of action of the remedy, the prompt subsidence of the splenic enlargement, the very pronounced decrease in the number of leucocytes, and the marked improvement in the general condition of the patients, were striking features in the effects produced. Of twelve patients referred to, eight had already been treated with the Roentgen rays, with no advantage or only temporary improvement. In each case radium, used as a last resort, had a marked effect on the spleen. Whereas, in the case of the Roentgen rays, strong irridiations cannot be long kept up in spite of thick filtering shields, lest the skin be injured, radium, with suitable filtration, can be left in the tissues for many hours without danger to the integument. The blood elements can therefore pass repeatedly through the spleen, which is under the influence of the radium rays and gradually absorbs the radiant energy imparted by the latter. The number of leucocytes undergoes a marked decrease in cases in which the Roentgen rays, already used, have lost their effect. In one of the author's patients whose general condition had already become desperate, the use of radium brought about so marked an improvement that pregnancy, some months later, was withstood without difficulty." Abstracted in N. Y. Med. Journ. July 17, 1915.

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CORRECTION.

Through an error in the table of the radioelements, shown on page 56 of the November number, the atomic weight of radium F is given as 206 instead of 210.

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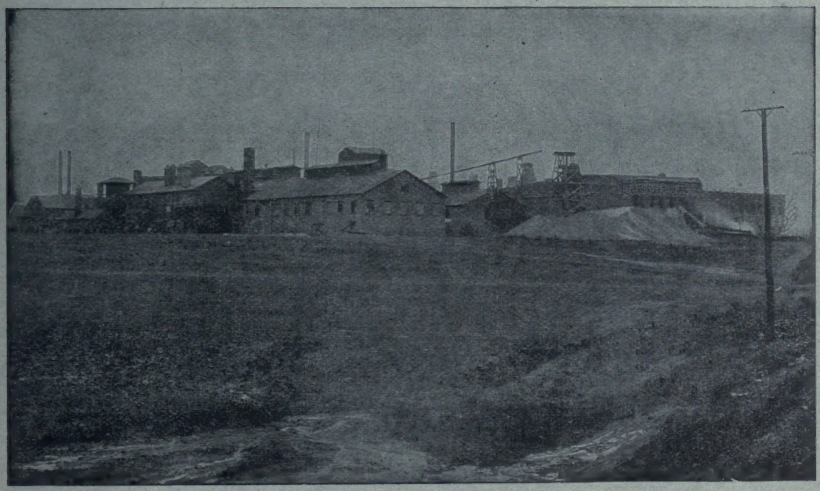

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